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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,412	07/11/2001	Shohei Koide	109.050US1	8219

21186 7590 05/04/2004

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,412	KOIDE, SHOHEI	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *9-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/2/04 has been entered.

Status of Claims

Claims 1-53 are pending in the application

Claims 1-8 and 51-53 are under examination.

Claims 9-50 are withdrawn from consideration as being drawn to non-elected invention.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 76, line 9. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to provide an adequate description of the claimed stabilized fibronectin type III (Fn3) molecule comprising a plurality of beta strand domains linked to a plurality of loop region sequences with one or more loop region sequences modified by deletion, insertion or replacement. It does not describe the kind, position and number of regions for each of the beta strand and loop regions. Nor does the means or kinds of linker between the two regions. Nor the length or number of plurality of the loop regions, the maximum number and/or kind of residues that can be modified by deletion, substitution or replacement, singly or in combination. More importantly, whether such modifications still retain the modified Fn3 ability to stabilize the Fn3 molecule. The specification at e.g., at page 76 provides a description for the specific triads that cause destabilization in the 10^{th} region of the Fn module. It also discloses ".....it is not clear why the destabilizing residues are almost completely conserved in Fnfn10. In contrast no other FN3 domains in human fibronectin contain this carboxyl triad. The carboxyl triad of FNfn10 may be involved in important interactions that have not been identified to date.....they could not perform stability measurements below

pH 5 due to protein aggregation, the pH dependence of TnFn3 resembles that of FNfn10…..FNfn3 does not contain the carboxylate triad at positions 7, 9 and 23 indicating that the destabilization of TNfn3 at neutral pH is caused by a different mechanism than that for FNfn10…..” As factually observed by applicant, there are just too numerous factors, variables and/or mechanisms necessary to identify the destabilizing regions for each kind of Fn in each species. In some species this may not even be present and therefore need not be modified, except for the pH being made acidic, in order to achieve a stabilizing effect. This would appear more complex in an Fn molecule that contains a plurality (e.g., a library of the different beta strands and loops linked by an infinite or unspecified amount of linkers, as claimed).

As applicant asserts in the REMARKS (page 16, paragraph one), the substitution of positively charged residues for other residues would not necessarily have a stabilizing effect on a protein. A change in charge of individual amino acid residues would have differing effects on proteins, all of which have unique conformational environments. For example, the newly cited Dao-pin is stated to teach that the introduction of an attractive electrostatic interaction has small effects on protein stability.

Claim Rejections - 35 USC § 112, second paragraph

Claims 1-8 and 51-53, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. In claims 1 and 51-52 the recited "more" is indefinite. --At least--is suggested.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 51-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7 of U.S. Patent No. 6,673,901 ('901 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other

because the instant claimed stabilized FnIII molecule comprising a plurality of fibronectin beta strain domains linked to a plurality of loop region sequences with the loop region varying by deletion, insertion and/or replacement is an obvious variant of the '901 patent. The claims in the '901 patent are similarly drawn to a fn3 polypeptide comprising of at least two Fn3 beta-strand domain with a loop region sequences linked to each other and the loop region varies by deletion, substitution and insertion of at least two residues and its ability to bind a specific binding partner. It is considered that the specific binding property of the '901 patent is a property obviously possessed by the instant Fn3 as the same compound is being claimed. Furthermore, the instant claimed stabilized mutation is a property obviously present in the '901 patent. The comparison made in the '901 patent with the wild type indicates that such modifications are made to stabilize a molecule.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5-6, 8 and 51-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Lipovsek for the reasons advanced in the last Office action.

Response to Arguments

Applicant argues that Lipovsek does not teach or suggest modified Fn3 molecule, wherein the Fn3 has a stabilizing mutation of one or more residues involved in unfavorable electrostatic interactions as compared to a wild-type Fn3, as recited by the present claims. Applicant disagrees with the statement that unfavorable interactions have to be removed in order for a compound to remain stable. For example, Bacillus subtilis CsbB protein contains a highly unfavorable electrostatic interaction between G1u3 and Glu66, but this protein is still predominantly folded at physiological temperature (Perl et al., 2000, Nature Structural Biology, 7, 380-383).

In response, Bacillus subtilis is an entirely different compound from Fn3. As Applicant asserted in the REMARKS the proper comparison is between a wild-type Fn3 and the modified Fn3 recited by the claim. Not between Fn3 (which is a mimic of an antibody) and an antibody, which is an entirely different

protein. It is therefore not seen how an entirely remote compound, as the argued, B. subtilis, which Fn is not even a mimic can be taken as a proper comparison.

Applicant argues that nowhere does Lipovsek teach that an Fn3 mutant has to be stable relative to the wild type to be physiologically useful. Lipovsek merely discloses that the mimics possess stability properties superior to antibodies. Again, the proper comparison that needs to be made is between a wild-type Fn3 and the modified Fn3, as recited by the claims. Further, Lipovsek does not teach or suggest modified Fn3 molecule, wherein the Fn3 has a stabilizing mutation of one or more residues involved in unfavorable electrostatic interactions as compared to a wild-type Fn3, as recited by the present claims.

In reply, applicant's attention is drawn at page 9, lines 6-11 of Lipovsek. It recites "…. the present antibody ***mimics*** exhibit improved biophysical properties, such as stability under reducing conditions and solubility at high concentrations…" The definition of the antibody mimic i.e., Fn3 is made relative to the natural or wild type Fn3, as provided at page 6, line 21 up to page 7, line 9. It is evident that when modification is made to a parent or wild type compound, the modified compound is compared to the unmodified or wild type one. This is the norm in

the art. Lipovsek only alludes to antibody comparison as to Fn mimics of its scaffold design. Attention is further directed to the comparison of the different Fn given in Figure 4. Also, to page 14,line 20 up to page 15, line 20 as to the different mutations made on the FNfn10 module. Regarding applicant's argument as to the mutated residues being involved in unfavorable electrostatic interactions, it is well settled that it is not invention to perceive that the product, which others have discovered, had qualities, which they failed to detect. Applicant is, in effect arguing that a structure taught by the prior art, and hence, potentially in possession of the public, is patentable to them because it also possesses an inherent but hitherto unknown function, which they claim to have discovered. This is not the law. A patent on such a structure would remove the public that which is in the public domain by virtue of its inclusion in the prior art. (In re Wiseman 201 USPQ 658). It is considered that the disclosure of Lipovsek of mutating several positions to form a stable Fn would indicate that these residues undergo unfavorable interactions. Accordingly, the specific disclosure of Lipvosek reciting the different specific residues in the Fnfn10 that has been modified fully meets the broad claimed modified Fn3 with stabilizing mutation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipvosek in view of Koide and Blaschuk (U.S. 6,391,855) for reasons set forth in the last Office action.

Response to Arguments

Applicant argues that the examiner rejected claims 1-3, 5-6, 8 and 51-53 as being anticipated (obvious, not anticipated) under 35 U.S.C. 103(a). Applicant concedes that one of ordinary skill in the art would have been able at the time that the application was filed to perform substitutions in a protein, and to determine whether the modified protein was more stable that the wild type application. Applicant asserts, however, that

the cited art does not contain a suggestion or incentive that would have motivated the skilled artisan to modify the references.

In response, attention is drawn to the disclosure of Koide at page 54, line 5 referring to the Dickinson reference which states that Arg stabilize Fn3. Thus, at the time of the invention, one having ordinary skill knows that positively charged residues such as the basic residues, Lys or Arg are known to have stabilizing effect on molecules such as Fn3 as taught by Koide. The substitutions (e.g., side chain modification) are positively taught by Blaschuk as conservative substitutions. (See col. 8, lines 53-66 i.e., Glu or Lys or Asp). A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties. One skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine. Such conservative substitutions are normally done in

structure activity studies of compounds to discovery lead compounds with improved properties relative to its parent compound.

The indicated allowability in the last Office action of claims 4 and 7 is withdrawn. It is evident from the 103 rejection, above, that the secondary references were applied or used for the claimed limitations recited in claims 4 and 7. The inadvertent omission of these claims in the rejection is regretted.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
May 1, 2004